REMARKS

Reconsideration of the Office Action mailed November 9, 2001, (hereinafter "instant Office Action"), entry of the amendments hereinabove, withdrawal of the rejection of claim 1 and reinstitution of claims 2-88, are respectfully requested.

In the instant Office Action, claims 1-88 are listed as pending, claims 2-88 are listed as withdrawn from consideration and claim 1 is listed as rejected.

Attached hereto as Appendix A is a marked-up version of the changes made to the claims by the current amendment. Appendix A is captioned **"Version With Markings To Show Changes Made"**.

The Examiner has made the restriction requirement final.

The Examiner has rejected Claim 1 under a judicially created doctrine as being drawn to an improper Markush group. The Examiner suggests that this rejection can be overcome by limiting claim 1 to just the elected group, namely Group 1 (formula 2). Applicants have amended claim 1 as suggested by the Examiner by deleting all of the formulas except formula 2, without waiver or prejudice to Applicants' right to pursue the cancelled subject matter in a divisional or continuation application. Therefore, the rejection of Claim 1 under the judicially created doctrine as being drawn to an improper Markush group is obviated and should be withdrawn.

The Examiner has withdrawn claims 2-88 from consideration "because art was found (see M.P.E.P. 803.02)". Applicants respectfully request that claims 2-88 be reinstated in view of the amended claim 1 submitted herewith, which has been narrowed to encompass the elected group as discussed hereinabove and, thus, does not claim any non-elected subject matter.

The Examiner has rejected claim 1 under 35 U.S.C. §112, second paragraph, for the reasons stated at page 4 of the instant Office Action. Applicants respectfully traverse this rejection. Applicants response to the Examiner's enumerated points are numbered accordingly to track the Examiner's points.

i) The Examiner alleges that it is not known what the terms "prodrugs" and "biologically active metabolites" are. Applicants respectfully traverse this rejection. Applicants point out that both terms are terms of art that are known to one of ordinary skill in the art. The inclusion of "prodrugs" in a claim is analogous to including the phrase "pharmaceutically acceptable salts thereof" (which the Examiner has not questioned) in that the metes and bounds of a prodrug are

as clear and definite to one skilled in the art as is the metes and bounds of the term "pharmaceutically acceptable salts thereof". It is clearly understood that a pharmaceutically acceptable salt of a claimed compound may be used in place of the claimed compound. With respect to the inclusion of "prodrugs" in a claim, the meaning of the term is equally clear in that "prodrug" refers to a compound that is converted a metabolic biotransformation and yet is biologically active, see Chapter 8, entitled "Prodrugs and Drug Delivery Systems," in The Organic Chemistry of Drug Design and Drug Action, by Richard Silverman, © 1992 Academic Press, San Diego (hereinafter "Silverman"), a copy of which is enclosed herewith for the Examiner's convenience as **Exhibit A**.

Silverman provides clear evidence that one of ordinary skill in the art is aware of the prodrugs that are commonly used in the art. Further, Silverman teaches how to make prodrugs generally. In addition, it is well known in the art of pharmaceutical chemistry how to make prodrugs. The chemistry of prodrugs is such that it is generally applicable and depends on the presence of functional groups and not the structure of the core compound.

With respect to the phrase "biologically active metabolites", Applicants note that this phrase is also known to those of ordinary skill in the art. It is well known that biologically active metabolites are those compounds that result when an administered compound is metabolized by the physiological system of a recipient and yet retain biological activity. Further, it is well known in the art how to isolate metabolites of an administered compound. For example, samples of urine and/or blood from *in vivo* test animals are collected, from which metabolites of the administered compound are identified and isolated by, for example, HPLC. The metabolites can then be tested in *in vitro* or *in vivo* assays to determine whether the metabolites are or are not active. Such testing entails routine experimentation and is well known in the art. Therefore, the term "biologically active metabolites" is definite and clearly understood by one of ordinary skill in the art.

ii) With respect to the term "substituted", Applicants direct the Examiner's attention to page 55, lines 11 to 24, of the specification, which provides a clear and definite definition of the term "substituted".

iii) With respect to the term "cycloalkyl", Applicants point out that it is a term of art that is well known to one of ordinary skill in the art. That is, the term represents cyclic moieties made

up of carbon atoms, which may be unsaturated but not to the point of unsaturation that would be considered to make the moiety aromatic; and encompasses a single ring system as well as polycyclic system, e.g., bicyclic, tricyclic, etc. Further, since the breadth of the term "cycloalkyl" is not limited in any way by the instant application, and there is no disclosure in the instant application that would cause confusion as to the definition of the term, the term "cycloalkyl" is clear and definite.

iv) With respect to the term "heterocyclic", Applicants direct the Examiner's attention to page 54, lines 8-25, which defines the term "heterocyclic". Such definition provides a clear and definite understanding of the metes and bounds of the term.

Based upon the foregoing, the rejection of claim 1 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

The Examiner has rejected claim 1 as allegedly being unpatentable under 35 U.S.C. §103(a) over Altmann et al. (WO 97/49706). Applicants respectfully traverse this rejection. Applicants point out that claim 1 must be considered in its entirety, that is, as the genus which is claimed. For example, one of the main differences between Altmann et al. and the compounds of claim 1 is that Altmann et al. do not suggest Applicants' R_2 group which is more complex than the simple moieties disclosed by Altmann et al. in the same position on their core structure. Since Applicants' R_2 group is present in all of the permutations of Formula (I), the entire genus of Applicants' claim 1 is not suggested by Altmann et al. From another viewpoint, Altmann et al. do not remotely suggest the full scope of amended claim 1. Therefore, Altmann et al. do not present a *prima facie* obviousness reference.

Based upon the foregoing argument, the rejection of claim 1 under 35 U.S.C. 103(a) over Altmann et al. (WO 97/49706) is overcome and the rejection should be withdrawn.

Applicants appreciatively note that the Examiner states at the bottom of page 5 "[t]he elected compound is allowable because the closest prior art reference of Altmann et al. (WO 97/49706) does not fairly teach nor fairly suggest a phenoxyphenyl group at R_1".

Based upon the foregoing, Applicants believe that claim 1, as amended, and claims 2-88, when reinstated, are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that there are any issues that could be resolved in a telephone conference, Applicants invite the Examiner to call Applicants' Attorney, John D. Conway at (508) 688 8046.

Respectfully submitted,

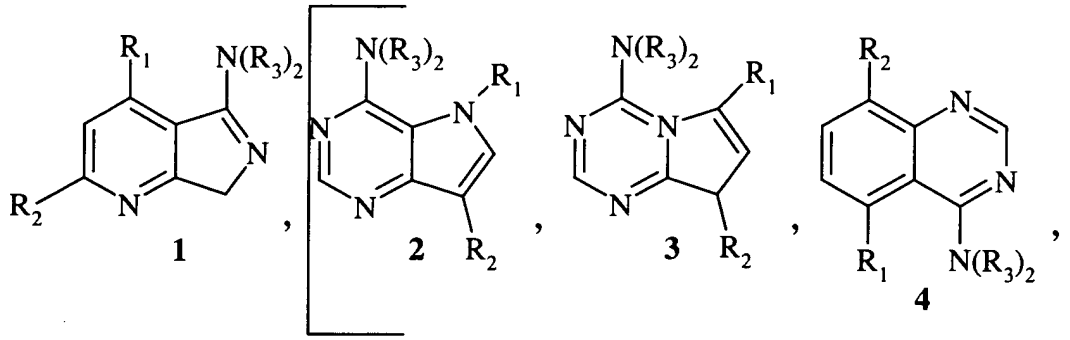
Date: August 20, 2002

Tara Seshadri
Agent for Applicants
Reg. No. 48,591
Abbott Bioresearch Center, Inc.
100 Research Drive
Worcester, MA 01605
(508) 688 8058

Appendix A

Version With Markings To Show Changes Made

1. (Amended) A compound of Formula (I), the racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof, [selected from the group consisting of]



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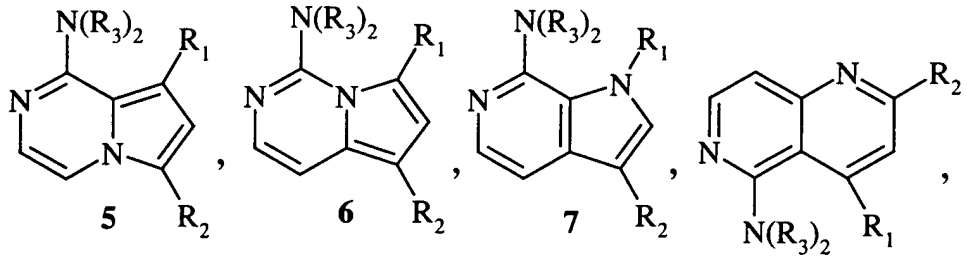

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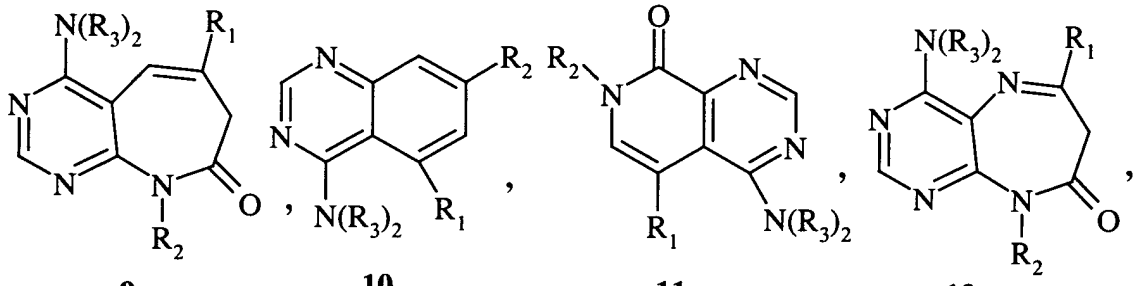

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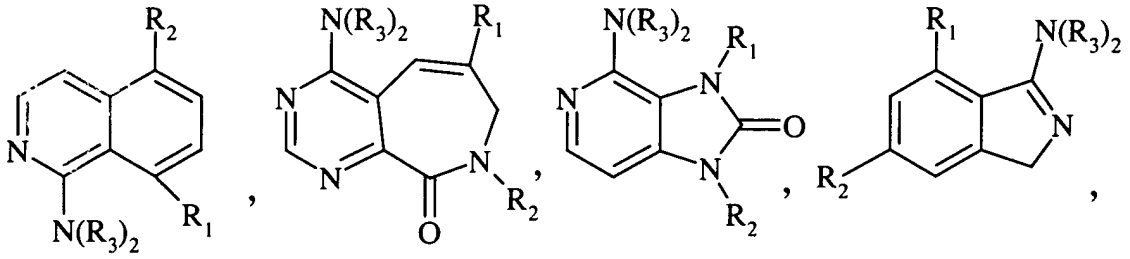

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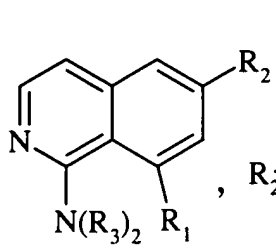

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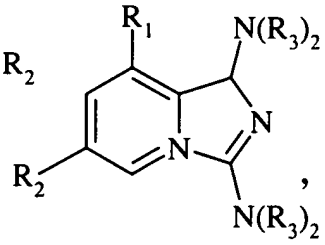

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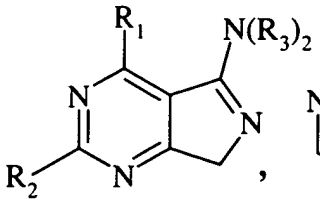

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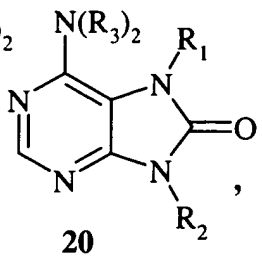

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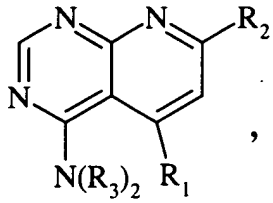

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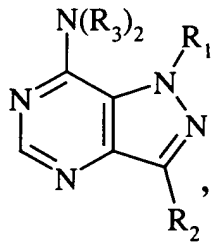

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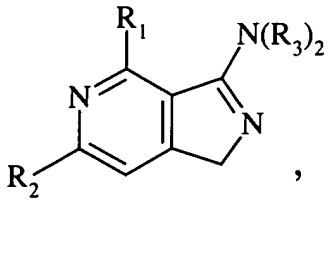

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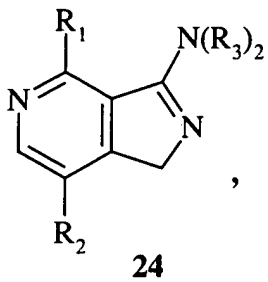

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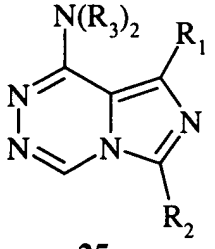

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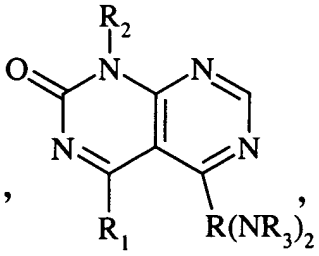

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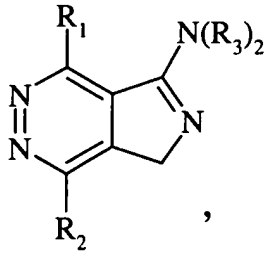

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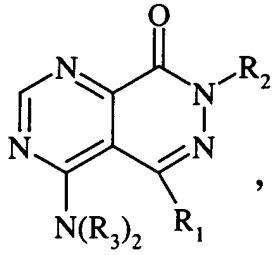

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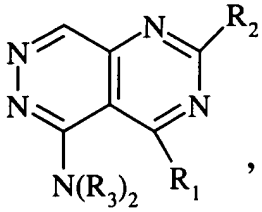

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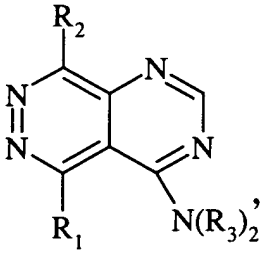

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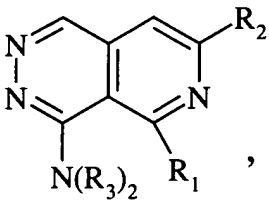

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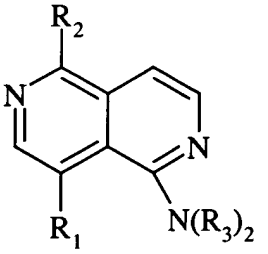

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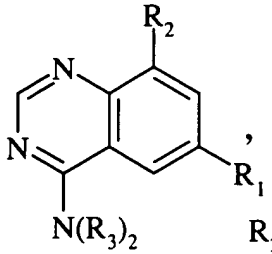

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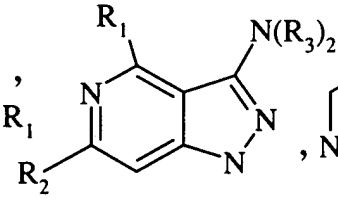

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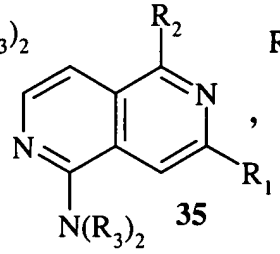

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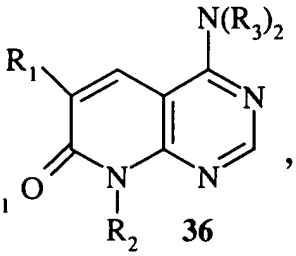

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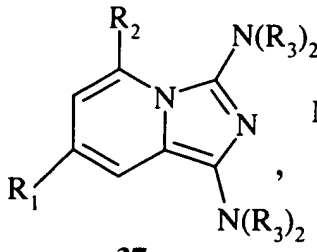

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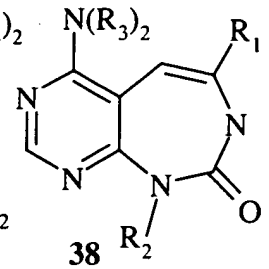

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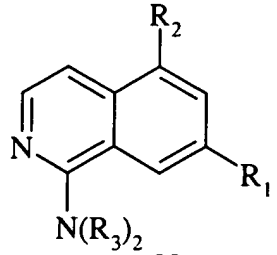

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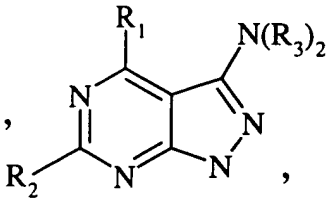

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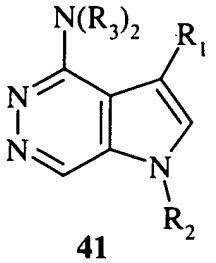

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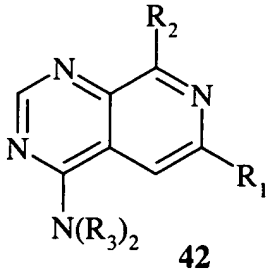

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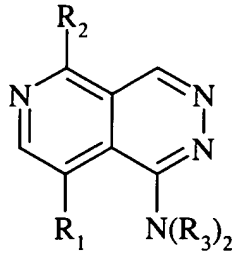

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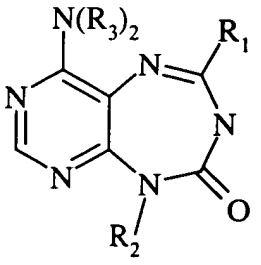

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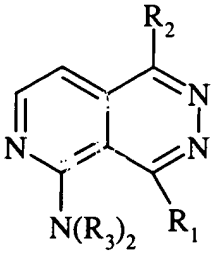

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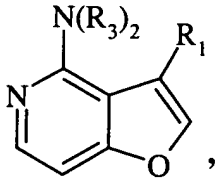

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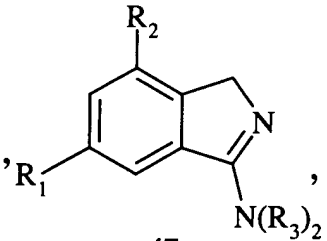

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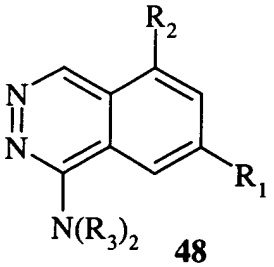

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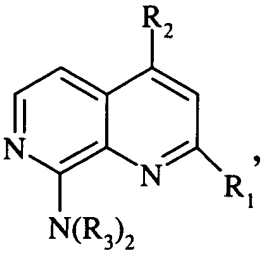

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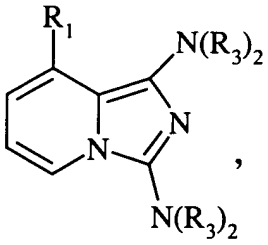

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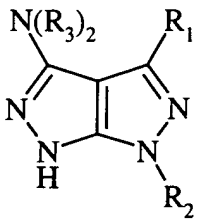

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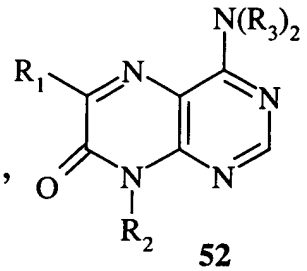

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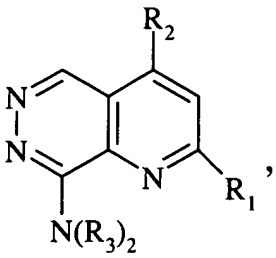

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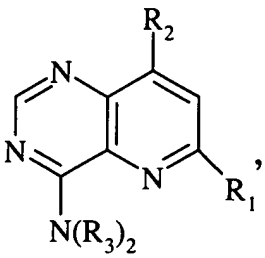

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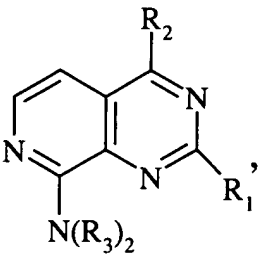

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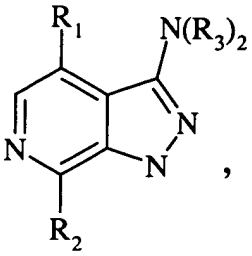

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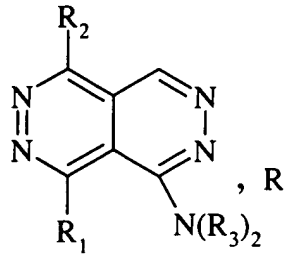

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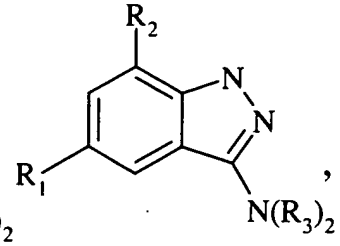

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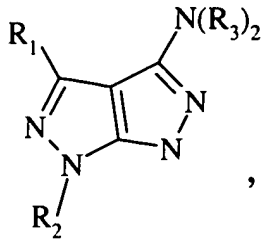

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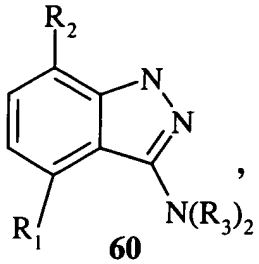

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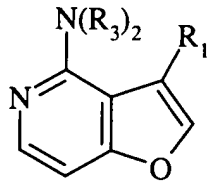

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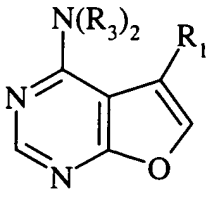

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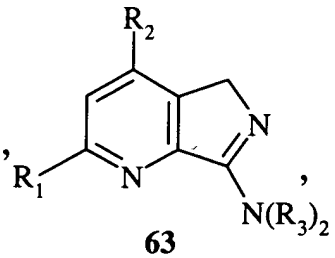

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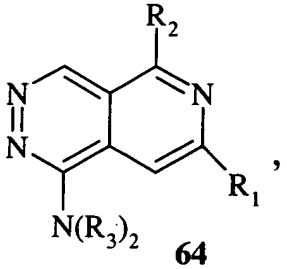

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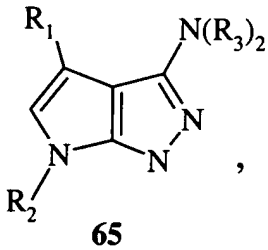

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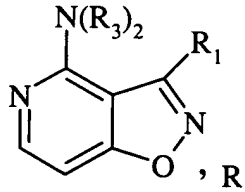

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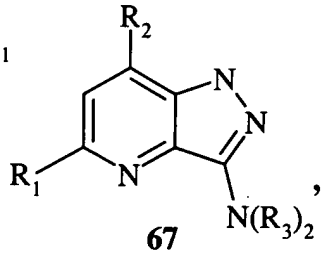

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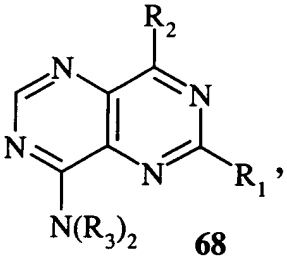

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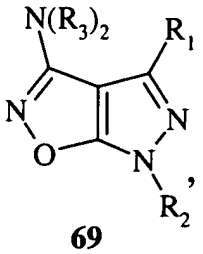

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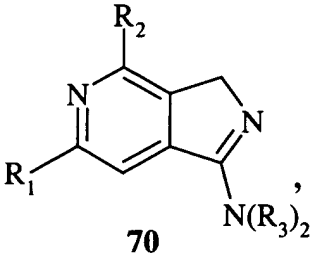

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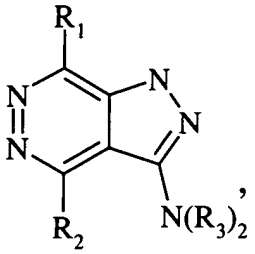

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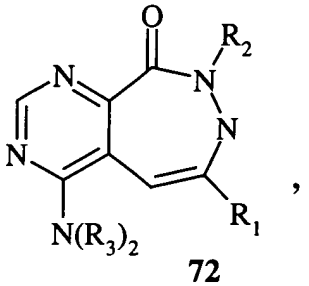

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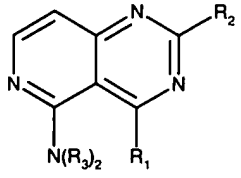

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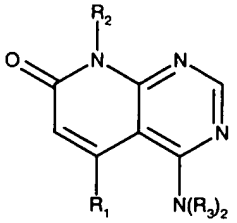

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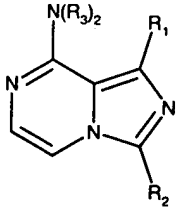

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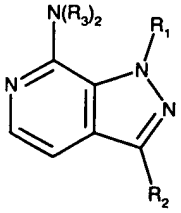

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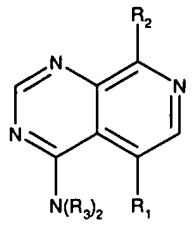

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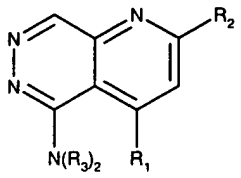

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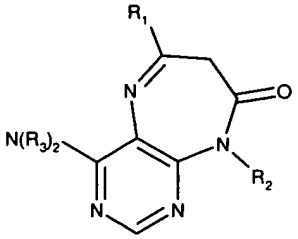

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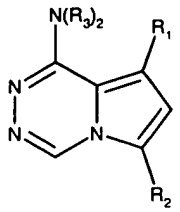

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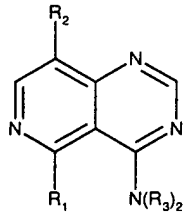

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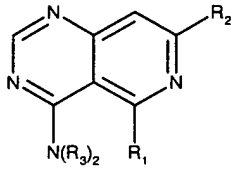

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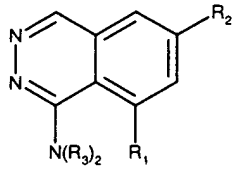

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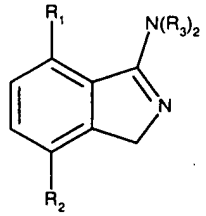

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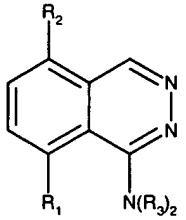

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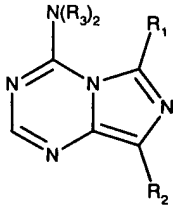

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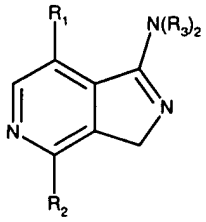

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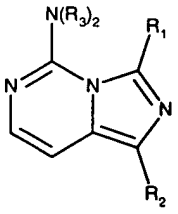

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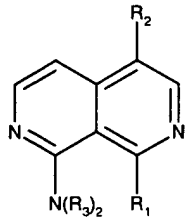

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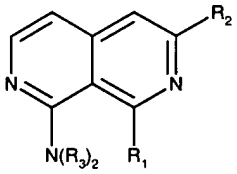

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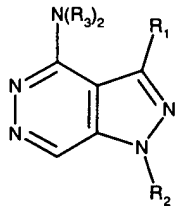

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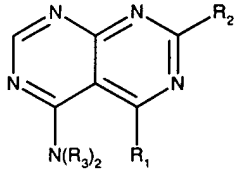

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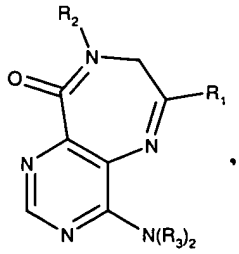

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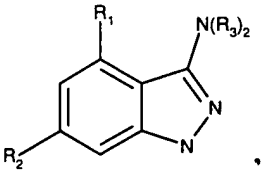

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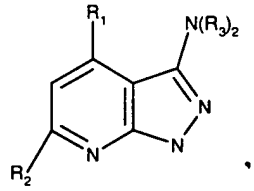

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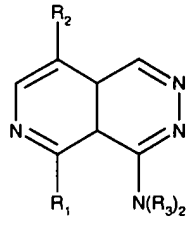

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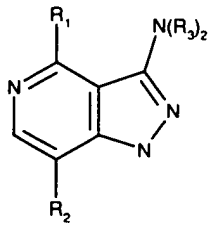

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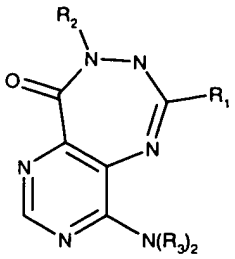

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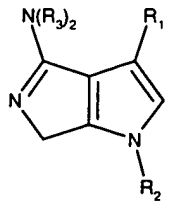

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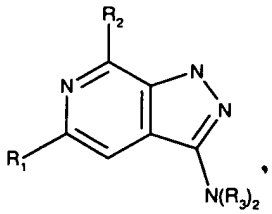

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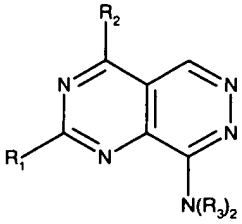

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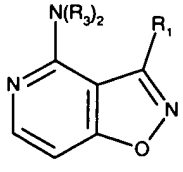

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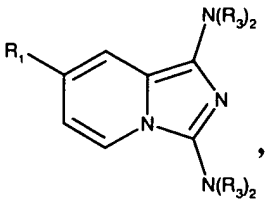

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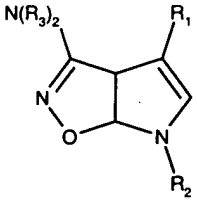

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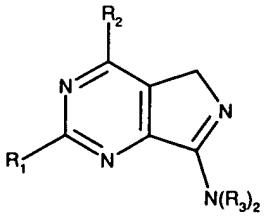

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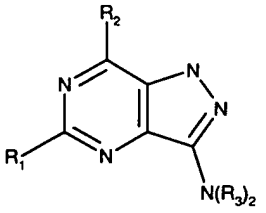

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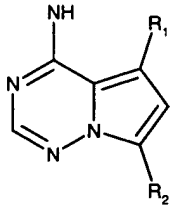

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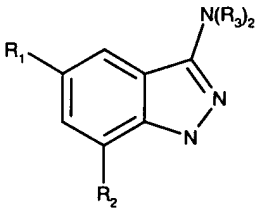

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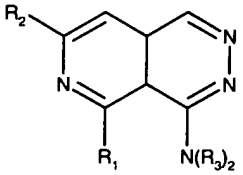

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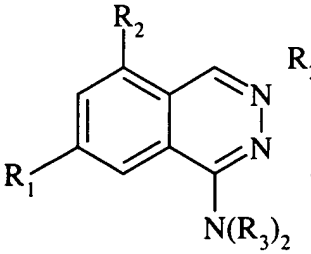

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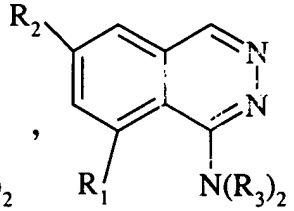

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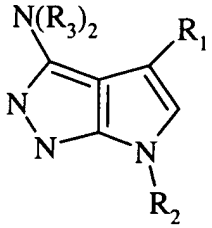

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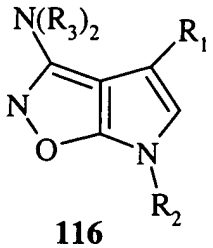

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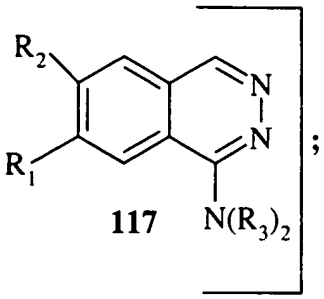
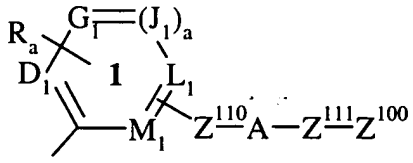
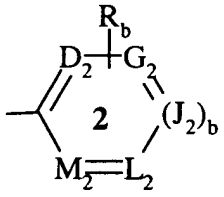
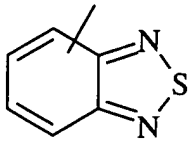
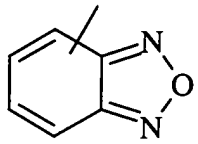


117

wherein:

R_1 is 

where Z^{100} is  or a group optionally substituted with R_b selected from the group consisting of cycloalkyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzothiazolyl,  ,  , thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, benzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN,

OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z^{105}-C(O)N$(R)_2$, -Z^{105}-N(R)-C(O)-Z^{200}, -Z^{105}-N(R)-S$(O)_2$-Z^{200}, -Z^{105}-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH_2-NR_dR_e, -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-Oalkyl, -W-$(CH_2)_t$-S-alkyl, or -W-$(CH_2)_t$-OH;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring; t for each occurrence is independently an integer from 2 to 6; W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl;

or R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 is hydrogen, hydroxy, substituted or unsubstituted alkyl or substituted or unsubstituted alkoxy;

A is -O-; -S-; -$S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; -N(SO_2R)-; -CH_2O-; -CH_2S-; -CH_2N(R)-; -CH(NR)-; -CH_2N(C(O)R))-;

$-CH_2N(C(O)OR)-$; $-CH_2N(SO_2R)-$; $-CH(NHR)-$; $-CH(NHC(O)R)-$; $-CH(NHSO_2R)-$; $-CH(NHC(O)OR)-$; $-CH(OC(O)R)-$; $-CH(OC(O)NHR)$; $-CH=CH-$; $-C(=NOR)-$; $-C(O)-$; $-CH(OR)-$; $-C(O)N(R)-$; $-N(R)C(O)-$; $-N(R)S(O)_p-$; $-OC(O)N(R)-$; ; $-N(R)-C(O)-(CH_2)_n-N(R)-$, $-N(R)C(O)O-$; $-N(R)-(CH_2)_{n+1}-C(O)-$, $-S(O)_pN(R)-$; $-O-(CR_2)_{n+1}-C(O)-$, $-O-(CR_2)_{n+1}-O-$, $-N(C(O)R)S(O)_p-$; $-N(R)S(O)_pN(R)-$; $-N(R)-C(O)-(CH_2)_n-O-$, $-C(O)N(R)C(O)-$; $-S(O)_pN(R)C(O)-$; $-OS(O)_pN(R)-$; $-N(R)S(O)_pO-$; $-N(R)S(O)_pC(O)-$; $-SO_pN(C(O)R)-$; $-N(R)SO_pN(R)-$; $-C(O)O-$; $-N(R)P(OR_g)O-$; $-N(R)P(OR_g)-$; $-N(R)P(O)(OR_g)O-$; $-N(R)P(O)(OR_g)-$; $-N(C(O)R)P(OR_g)O-$; $-N(C(O)R)P(OR_g)-$; $-N(C(O)R)P(O)(OR_g)O-$, or $-N(C(O)R)P(OR_g)-$;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_g for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2;

or in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_g together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1;

R_2 is $-Z^{101}-Z^{102}$;

Z^{101} is a covalent bond, $-(C_1-C_6)-$, $-(C_1-C_6)-O-$, $-(C_1-C_6)-C(O)-$, $-(C_1-C_6)-C(O)O-$, $-(C_1-C_6)-C(O)-NH-$, $-(C_1-C_6)-C(O)-N((C_1-C_6))-$ or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen, a substituted or unsubstituted alkyl group, a substituted or unsubstituted cycloalkyl group, a substituted or unsubstituted, saturated or unsaturated heterocyclic group, or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group;

said substituted heterocyclic or substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, substituted or unsubstituted alkoxy, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido; substituted or unsubstituted amino, oxo, a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more nitrogen atoms, one or more oxygen atoms or a combination thereof;

wherein said nitrogen atoms are independently optionally substituted by a substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl group; or

R_2 is of the formula B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalklylcarbonyl, hydroxy, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted azacycloalkyl, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group

consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6.